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Homocysteinemia and Depression in Community-Dwelling Older Adults: The Cohort Longitudinal Study "InveCeAb" (Brain Aging in Abbiategrasso)

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Abstract

Depression is a major health problem, especially for elderly people. According to the "homocysteine hypothesis of depression", high homocysteine levels may cause depression of mood via cerebrovascular diseases. Whilst biologically plausible, such hypothesis needs yet confirmation. We aimed at: 1) studying the relationships between homocysteinemia (HCY) and depression in a community-dwelling cohort of people aged 70 to 75 years at baseline; 2) investigating plasma levels of HCY and 3) comparing these levels between males and females, in the same population. We exploited the data from four waves (2010, 2012, 2014 and 2018) of the longitudinal study "InveCeAb", with specific regard towards mood assessment, by Geriatric Depression Scale (GDS) scoring, and diagnosis of clinically relevant or subthreshold depression. HCY plasma levels were measured in the waves 2012, 2014 and 2018. Sample attrition was due mainly to death or overall worsening. No statistically significant differences were found in plasma homocysteine levels in each wave, according to depressive symptoms. No correlations were found between plasma HCY levels in each wave with their corresponding GDS scores, even after adjustment for folate and cobalamin blood concentrations. Dichotomized levels of HCY (≤15 vs >15 μM/l) were not associated with dichotomized GDS scores (≤4 vs higher), clinically relevant and subthreshold depression diagnosis and any antidepressive use, in any wave. First (2012) HCY levels increased with participants' increasing age, cross-sectionally. Listwise HCY concentrations decreased along the 3 waves. HCY levels were always higher in males than in females. Our results may challenge the "homocysteine hypothesis" of depression, whilst supporting the role of high homocysteine-

mia as a marker of overall bad health.

Keywords

Homocysteinemia, Depression, Aging, Cohort

1. Introduction

Total plasma levels of the aminoacid homocysteine (tHcy) are associated with several physiologic and lifestyle factors and common diseases. Increasing age, male sex, smoking, coffee consumption, high blood pressure, unfavorable lipid profile, high creatinine, and the MTHFR 677C T polymorphisms are among the factors associated with increased tHcy levels; physical activity, moderate alcohol consumption, and a good folate or vitamin B-12 status are associated with lower tHcy levels. Subjects with raised tHcy levels have increased risk of cardiovascular morbidity, cardiovascular and noncardiovascular mortality, and are more likely to suffer from depression and from cognitive deficit (elderly).

Many studies found an association between depression and tHcy or B-vitamin status, but, often, the relation was weak and sometimes disappeared in multivariate analyses. For example, in a community-based study conducted in Western Norway, there was a weak concentration-response relation between tHcy and depression score and risk of depression. The association was strongest for those with tHcy > 15 μM/l, as they had 2-fold higher risk of having depression compared with subjects with tHcy < 9 μM/L [1].

Depression is a major cause of disability, affecting more than 300 million people (about 4.4% of the whole world's population) [2] [3].

According to the World Health Organisation (WHO), predictions indicate that by 2030 depression will be the leading cause of disease burden globally [4]. Depression is ranked by WHO as the single largest contributor to global disability (7.5% of all years lived with disability in 2015) [3].

"The term depression is used variously to refer to depressed mood, which may or may not be part of a cluster of signs and symptoms constituting a depressive syndrome or episode. A depressive episode may or may not qualify for a diagnosis of a depressive disorder, including but not limited to major depressive disorder and dysthymia. The term 'clinically depressed' is also sometimes used to denote a depressive syndrome warranting clinical attention" [5].

Major depressive disorder is one of the most common mental health disorders and is a leading contributor to disability worldwide [6].

Depression is a problem of major public health importance in late life too [5].

Overall, the prevalence of depression ranges from 8.8% to 18.3% in people aged 60 years or older [7]. In community-dwelling elderly patients, prevalences of depressive symptoms and major depressive disorder are 15% and 1% to 3%, respectively [5].

The prevalence of depressive symptoms in community-dwelling healthy older populations varies significantly worldwide, being of 9.8% in Australia and US [8].

In a systematic review, the incidence rate of major depression in the population 70 years of age and older was 0.2 - 14.1/100 person-years, and incidence of clinically relevant depressive symptoms was 6.8/100 person-years. Female incidence was mostly higher than male [9].

Late-life depression (LLD) refers to major depressive disorder that is present in individuals 60 to 65 years and older and can be early onset or late onset. Late-life depression is becoming a major public health concern, because of its detrimental effects both for individuals and society. LLD is associated with cognitive impairment and high rates of comorbidity, including cardiac and cerebrovascular disease and stroke, as well as increased risk of obesity, diabetes, frailty, and neurodegenerative diseases, such as Alzheimer disease and vascular dementia. LLD affects 1.8% to 7.2% of older adults in the general community [6].

Many risk factors may lead to depressive disorders, such as gender, age, co-occurrence with other mental disorders, cardiovascular disease and increased chemical compounds that perturb neurotransmitters [2]. Knowledge of the etiology of depression would lead to prevention and knowledge of pathogenesis would lead to a cure.

The pathogenesis of LLD includes insufficient monoamine neurotransmission, increased inflammation, abnormal glutamate input, decreased neurotrophic factor production/high methylation, and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Further, age-related amyloid beta deposition and low diversity of the gut microbiome might result in LLD with cognitive impairments [8].

As depressive disorders may derive from perturbed neurotransmission, elevated plasma homocysteine, also known as hyperhomocysteinaemia, may be involved. Hyperhomocysteinaemia may lead to abnormal neurological functions by interfering with neurological functioning in various ways, like excitotoxicity, DNA damage, oxidative stress and inflammation [2]. Therefore, it has been suggested that hyperhomocysteinaemia can increase the risk of depression.

According to the "homocysteine hypothesis of depression", genetic and environmental factors elevate homocysteine levels, which cause vascular disease of the brain, and/or transmitter alterations, which cause depression [10].

In a cross-sectional study of a community-representative sample of 4.204 men aged 71 - 89 years, high plasma homocysteine (above 15 μM/L) had the highest Population Attributable Fraction (PAF) for depression (PAF: 15%, 95% confidence interval [95% CI]: 5% - 23%), assuming the relationship is causal. The association of depression, defined by a Geriatric Depression Scale 15 items score of 7 or greater, with high plasma homocysteine overcame those with other cardiovascular disease and risk factors like history of diabetes, angina, myocardial infarction, and stroke; current smoking; triglycerides and MTHFR677 genotype

[11].

Hyperhomocystemia (HCY > 15 μM/l) was detected in 35% of patients, more frequently in men (52%) than in women (31%) during acute episode of bipolar depression, in Polish people aged 20 - 78 (mean 51 ± 13) years [12].

Hyperhomocysteinemia (HHcy), usually defined as total homocysteine (tHcy) concentrations > 15 μmol/L, has been associated with many non-communicable diseases (NCDs), including cardiovascular and cerebrovascular diseases, type 2 diabetes, and cancers. In a systematic review, harvesting a total of 36 studies consisting of 60.754 Chinese subjects (57.3% male; age range, 3 - 97 years), the overall pooled prevalence of HHcy was 27.5%. The prevalence increased with age and was significantly higher in men than in women [13]. These results are in keeping with those obtained in a totally different context, like western Norway [1].

Yet, the literature about the relationships between the levels in plasma homocysteine and depression is inconsistent, so that the issue is still a matter of debate.

Therefore, in this still loosely defined scenario, we aimed at: 1) shedding light on the relationships between homocysteinemia and depression (depressive symptoms, diagnosis of clinically significant or subthreshold depression) in a community-dwelling cohort of people aged 70 to 75 years at baseline (main research question); 2) investigating plasma levels of homocysteinemia and 3) comparing these levels between males and females, in the same population (secondary research questions).

2. Materials and Methods

2.1. Sample and Assessment

We leveraged the data of the longitudinal study "InveCeAb" (Brain Aging in Abbiategrasso). The "InveCeAb" study is set in Abbiategrasso, a small city in the province of Milan (Northern Italy) with 30,000 inhabitants. The eligible population comprises all people born between 1935 and 1939 who were residents living in Abbiategrasso on the start date of the study (1,773). Following a single age quintile in a longitudinal study format allows us to minimize the confounding effect of age. The study is being conducted in a specific geographic area; hence, the recruited cohort is homogeneous with respect to age and ethnicity. Moreover, the choice to study individuals aged 70 - 74 years is based on the observation that this is considered to be a "transitional age" between late adulthood and old age, especially in terms of cognitive function, and that social and lifestyle factors still influence cognitive aging during this time. We exploited the data of multidimensional assessments of the waves 2010, 2012, 2014 and 2018. Through a careful and personalized recruitment process of contacts, at the starting of the enquiry, we got a high rate of adhesion: 80.35%. A list of eligible people was obtained from the municipal registry office. Prior to conducting follow-up measures, this list will be updated for relevant changes (e.g. hospitalizations, deaths,

and others) with the help of local health authorities, municipality, hospitals and general practitioners). Each phase of research was under the supervision of the "Federazione Alzheimer Italia" (Alzheimer Federation Italy), the key association supporting those affected by dementia and their relatives in Italy. Recruitment was conducted with the involvement of local social networks and voluntary associations. The design and aims of the survey were described in local newspapers and discussed in meetings with general practitioners, parishes, and volunteer organizations. All eligible individuals received a letter inviting them to attend a public presentation about the "InveCeAb" study. Public presentations about the survey were carried out separately for each cohort by birth-year (1935, 1936, 1937, 1938, 1939). During these meetings the first voluntary candidates were recruited. Those who did not volunteer to participate during the meetings received a letter explaining the study aims and inviting them to participate with a confirmed appointment date. They were also contacted by phone if their phone number was available. The longitudinal phase included all participants who participated to the cross-sectional assessment, excluding those who have since passed away, have moved to another city, or those who are no longer willing to participate to the study. The details of the methodology are extensively described elsewhere [14]. Briefly, the multidimensional geriatric assessment includes a broad anamnesis, a medical examination, a neuropsychological battery, and a blood collection. The presence of depressed mood was evaluated as part of the medical and neuropsychological assessment. The history of depression and taking antidepressant drugs were specifically investigated by the collection of the anamnesis. Specifically, a diagnosis of depression was assigned when the clinical evaluation confirmed the presence of at least three of the following criteria: 1) a history of depression, 2) antidepressant therapy, 3) a score of 8 or more out of 15 on the Geriatric Depression Scale (GDS) [15], and 4) the positive answer to two key questions on depressed mood, which were derived from the CES-D scale and have been used in epidemiological studies. These two questions were: "During the past month, have you often been bothered by feeling down, depressed, or hopeless?" and "during the past month, have you often been bothered by little interest or pleasure in doing things?" [16]. Otherwise, the presence of "depressive symptoms" was considered to be "subthreshold depressive symptoms" [17], as described by the National Institute of Clinical Excellence (NICE) [18]. For the analyses concerning the GDS 15 items scale uniquely, here we adopted the standard cutoff for 15 items GDS: normal score is 0 - 4 [19] [20].

2.2. Laboratory

Venous blood samples were collected by venipuncture at between 0800 and 0930h after an overnight fast. Serum was separated from whole blood using BD Vacutainer® SST II Advance tubes (Becton Dickinson, Oakville, ON, USA). Serum tHcy, folate and cobalamin levels were determined by chemiluminescent microparticle immunoassay on an Architect 2000 analyser (Abbott, Abbott Park,

IL, USA) within 3 h of blood collection.

2.3. Statistical Analysis

Descriptive as well as inferential analyses [cross tabulations and non-parametric comparisons (McNemar for GDS and depression diagnosis; Mann-Whitney U or Friedman's test, as appropriate for research questions 1, 2 and 3; Spearman Rho for research question 2)] were performed by the software SPSS version 20. Alfa was set at 0.05.

2.4. Statements and Declarations

Competing interests: The authors declare that they have no competing interests.

Ethics approval: All methods were carried out in accordance with the Declaration of Helsinki and following amendments. The study protocols were approved by the Ethical Committee of the University of Pavia—waves 2010, 2012, 2014 (Protocol 3/2009) and by the Ethics Committees of the Fondazione IRCCS Policlinico San Matteo, Pavia, wave 2018 (Protocol 20180049197).

The paper follows the recommendations by STROBE guidelines for reporting observational studies [21].

3. Results

3.1. Overall

At baseline evaluation (2010), 1,321 participants were recruited: 54% were female; mean (standard deviation), median and modal ages were 72 (2.3), 72 and 71 years, respectively. Along the subsequent waves, the sample shrinked to 1,062 (2012), 935 (2014), 697 (2018) subjects. The attrition was due in most cases to deaths, or to severe deterioration of health status hindering the participation. The flow of the participants throughout the four waves of the longitudinal observation is shown in **Figure 1**.

In all the 4 waves, most participants had GDS scores within the normal cutoff (0 - 4): 84.2% (2010), 82.9 (2012), 80.2% (2014), 73.1% (2018); yet the decrease in % percentages of people with normal GDS scores was significant ($p < 0.0005$ for all McNemar's comparisons). The percentages of participants with clinically relevant depression increased during the 8 years of observation: 5.6% (2010), 6.1% (2012), 7% (2014: McNemar $p = 0.013$ vs 2010), 11.7% (2018: McNemar $p < 0.0005$ vs 2010). The prevalence of subthreshold depression showed some fluctuations throughout the 4 waves: 15.2% (2010), 12.4% (2012: McNemar's $p = 0.025$ vs 2010), 14.4% (2014), 18.1% (2018).

Plasma homocysteine levels were measured during the 3 waves 2012, 2014 and 2018; their distributions were right skewed, so that their respective concentrations (μM/l) [median (interquartile range)] were: 15.7 (13 - 19.4) for year 2012; 15 (12.6 - 18.5) for year 2014; 14.2 (11.8 - 17.7) for year 2018. Therefore, in some inferential statistical analyses homocysteinemias were log-transformed. Percentages of people with hyperomocysteinemia (HCY > 15 μM/l) were: 55.2 (2012),

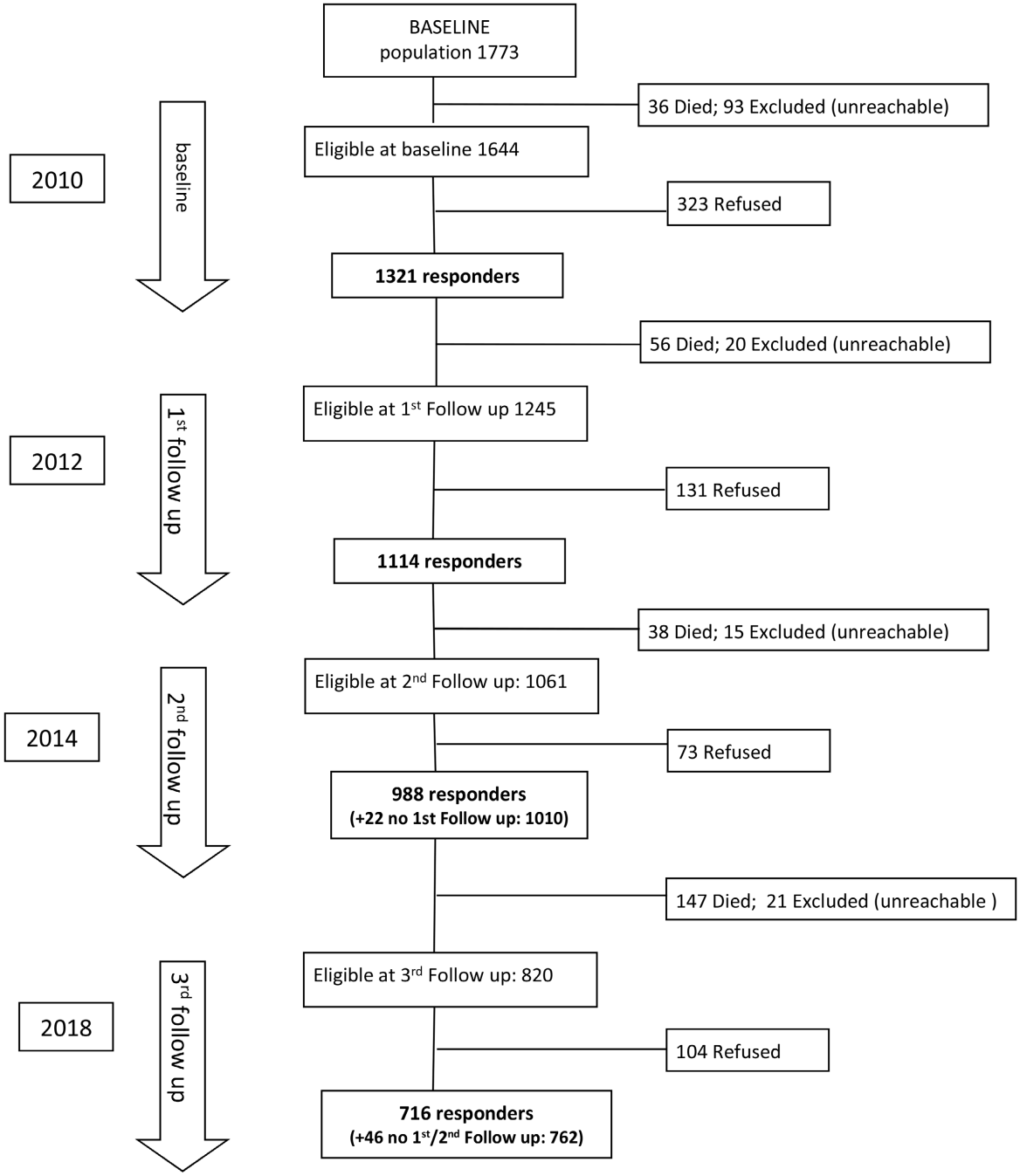

Figure 1. InveCe.Ab Study participants flow chart 2010-2018 (4 waves).

49.6 (2014) and 44.1 (2018).

3.2. Research Question 1

Plasma homocysteine levels along the 3 waves (2012, 2014 and 2018) according to GDS dichotomized classes are reported in **Table 1**.

No statistically significant differences were found in plasma homocysteine levels, even after logarithmic transformation, in each wave, when comparing people whose GDS scores were above versus below the cutoff (≤4), in the corresponding

wave.

Plasma homocysteine levels in the 3 waves were not correlated to their corresponding GDS scores, even after adjustment for folate and cobalamin blood concentration. Homocysteinemia dosed in 2012 was not correlated either with 2010 GDS scores or with the scores of the subsequent waves (2014, 2018).

The only statistically significant differences were found, in the last wave (2018) in plasma homocysteine levels according to the diagnosis of subthreshold depression, through non-parametric (Mann-Whitney U) tests ($p = 0.03$ either for crude or log-transformed values). However, the results went against expectations and showed higher homocysteine levels (μM/l) for people who were not diagnosed with subthreshold depression [median 14.7 (interquartile range 12 - 14.7)].

Further, after dichotomizing each waves' plasma homocysteine levels in two categories (≤15 vs >15 μM/l), crosstabulations with respective dichotomized GDS, clinically relevant and subthreshold depression diagnosis and any antidepressive use gave no statistically significant results.

3.3. Research Question 2

Plasma HCY concentrations as a function of participants' age at first blood collection (wave 2012) are reported in Table 2.

Homocysteinemia at its first measurement (wave 2012) was positively correlated with participants' age ($p < 0.0005$ by Spearman Rho); yet the regression explains only a very small amount of the variance ($R^2 = 0.009$).

Listwise plasma HCY concentrations along the 3 waves (680 cases) are reported in Table 3.

Table 1. HCY plasma concentrations in 3 InveCeAb waves as a function of GDS dichotomized levels.

Wave	GDS 0 - 4		GDS 5 - 15		p#
	HCY Median*	HCY Interquartile range*	HCY Median*	HCY Interquartile range*	
2012	15.6	13 - 19	16.2	13.6 - 20.8	0.091
2014	14.9	12.5 - 18.3	15.6	12.6 - 20.1	0.08
2018	14.25	11.8 - 14.775	14.3	11.8 - 17.775	0.978

*HCY plasma concentrations expressed in μM/l; #Mann-Whitney U test.

Table 2. Plasma HCY according to age at first blood collection (wave 2012)#.

Age at blood collection	72	73	74	75	76
HCY [median (interquartile range) in μM/l (wave 2012)]	15.05 (12.8 - 18.2)	14.9 (12.9 - 18.7)	16.5 (13.5 - 20.2)	16.6 (13.4 - 20.2)	17.6 (13.7 - 22.6)

#Anova: $F = 9.85$ ($p = 0.002$).

Table 3. Listwise plasma HCY concentrations (680 cases) along the 3 waves (2012, 2014, 2018)[#].

Wave	HCY Median (μM/L)	HCY Interquartile range (μM/L)
2012*[§]	15.4	9.8 - 21
2014[§]	14.8	8.9 - 23.7
2018*	14.25	8.25 - 20.25

[#]p by Friedman's test (post-hoc analysis); *2012 vs 2018: $p < 0.0005$; [§]2012 vs 2014: $p < 0.0005$.

In 680 listwise cases, plasma homocysteine levels decreased from the first measurements onward ($p < 0.0005$ by Friedman's test); a post-hoc analysis found statistically significant differences between concentrations in 2012 versus 2014 and 2018; all plasma homocysteine levels in these 680 listwise cases were highly correlated ($p < 0.0005$ for all Spearman Rhos) along the three waves (2012, 2014 and 2018).

3.4. Research Question 3

Within each of the three waves, plasma homocysteinemia levels (μM/l) [median (interquartile ranges)] were higher in males than in females ($p < 0.0005$): males 2012 = 16.8 (14 - 20.2)/females 2012 = 14.3 (12.1 - 16.9); males 2014 = 15.6 (13.3 - 19.4)/females 2014 = 13.9 (11.6 - 16.6); males 2018 = 15.4 (12.7 - 18.9)/females 2018 = 13.4 (11.1 - 16.8).

4. Discussion

The main results answered the three research questions:

Question 1: No statistically significant differences were found in plasma homocysteine levels, even after logarithmic transformation, in each wave, according to depressive symptoms;

Question 2: Homocysteinemia at its first measurement (wave 2012) was significantly correlated with participants' age. In listwise analysis plasma homocysteine levels decreased from the first measurements onward ($p < 0.0005$);

Question 3: Within each of the three waves, plasma homocysteinemia levels were higher in males than in females ($p < 0.0005$).

The total estimated number of people living with depression increased by 18.4% between 2005 and 2015 [22]. Prevalence rates vary by age, peaking in older adulthood (above 7.5% among females aged 55 - 74 years, and above 5.5% among males) [3].

Such a burden imposes the endeavor to go on with the research of potentially modifiable factors contributing to depression. Hyperomocysteinemia may be part of these factors, according to the "homocysteine hypothesis of depression" [10] [23].

High levels of the sulfur-containing *α*-amino acid homocysteine can be produced by impaired renal function, smoking, lack of physical activity, high blood

pressure and hyperlipidemia, as well as by excessive alcohol intake, high coffee intake and vitamin B12 and folate deficiency [2].

Homocysteine in the central nervous system is pivotal in two metabolic pathways including methionine and 5-methyltetrahydrofolate, which in turn contribute to the synthesis of neurotransmitters, such as serotonin, noradrenaline, and dopamine, so that the link between these cycles and depression is biologically plausible [24].

The "homocysteine hypothesis of depression" was born about 20 years ago [25]. This hypothesis claims that genetic and environmental factors elevate homocysteine levels, which cause vascular disease of the brain, and/or transmitter alterations, which cause depression [10]. According to such hypothesis, 15% of cases could be attributed to high tHcy, assuming the relationship is causal. In the Health in Men Study, the odds ratio (OR) of prevalent depression increased 4% (OR, 1.04; 95% confidence interval [CI], 1.02 - 1.05) with every unit increase of tHcy (micromoles per liter). It has been envisaged that lowering tHcy by 0.19 mg/L could reduce the odds of depression by about 20% [24]. Treatment with certain B vitamins demonstrably reduces homocysteine concentration. Fortification with folic acid decreased mean total homocysteine concentration and the prevalence of high homocysteine concentrations, in the Framingham Offspring Study cohort [26]. Voluntary fortification of foods with folate in Australia has been followed by a substantial increase (38%) in serum folate and decrease (21%) in tHcy in the general population [27]. Depression has been relieved by lowering homocysteine levels with B vitamin supplementation, in 127 patients attending 19 general practitioners with a special interest in depression [28]. In the B-VITAGE randomised, double-blind, placebo-controlled trial, B vitamins did not increase the 12-week efficacy of antidepressant treatment, but enhanced and sustained antidepressant response over 1 year, among 153 middle-aged and older adults [29].

In a systematic review with meta-analysis of observational studies, homocysteine level was higher in subjects with depression in comparison with healthy controls (weight mean difference = 2.53 μM/l, 95% confidence interval: 1.77, 3.30). Participants with hyperhomocysteinaemia had a higher chance of depression (Pooled risk = 1.34, 95% confidence interval: 1.19, 1.52). The depression diagnostic tool was a source of heterogeneity: hyperhomocysteinaemia yielded a significantly higher risk of depression, when GDS was employed as a tool for depression assessment. Noteworthy, such meta-analysis was centered on old people in 4 out of 26 studies; more, cohort studies were 5, whereas the other designs were cross-sectional (18) and case-control (3) [2]. In a meta-analysis of 9 cross-sectional studies that investigated the association between homocysteine and depression, the pooled odds ratio of depression among people with high plasma total homocysteine concentrations equals 1.70 (95% confidence interval, 1.38 - 2.08). This meta-analysis included mostly middle-aged and elderly people, recruited in community settings (8 studies) except hospital for one study [24].

As for the first research question, our results too don't support the "homocysteine hypothesis of depression", even taking account of folate and cobalamin levels.

Yet not all studies, however, have found an association between homocysteine and depression. Inconsistent results may be due to factors such as variations in diet and vitamin supplementation, which can affect folate intake, which in turn influences homocysteine concentrations. Genetic, socioeconomic, and familial factors, such as shared environment, could also have confounded findings of an association. The study of twins in clinical research has been useful in controlling for confounding factors. The Twins Heart Study (THS) included 180 twin pairs, 93 monozygotic and 87 dizygotic pairs, from the Vietnam Era Twin (VET) Registry, a large registry of middle-aged male-male twins, born between 1946 and 1956 and free of symptomatic cardiovascular disease, who served in the United States military during the Vietnam War. The findings from the THS were not consistent with a causal role for elevated homocysteine in the development of depression [30].

Most studies examining the association between depression and tHcy have been performed in developed countries. In order to fill the gap towards low-middle income countries, the Maracaibo Aging Study (MAS) recruited 1,418 participants aged 55 years and older. Participants with depressive symptoms had higher levels of tHcy than those without (15.1 versus 13.9 μmol/L; $p = 0.009$). In the fully adjusted model, taking account of sex, education, smoking, diabetes, hypertension, alcohol intake, stroke, and dementia, elevated tHcy levels were associated with depressive symptoms (OR = 1.58; 95% CI, 1.18 - 2.12). Yet, in this sample of older Hispanic, the association became borderline non statistically significant over age 66 ($p = 0.052$) [31].

240 men and 217 women from a population-based cohort aged ≥ 65 years were assessed 4 years later for depression (Geriatric Depression Scale, GDS ≥ 10/30 or use of antidepressants) in the Conselice Study of Brain Aging (CSBA), a population-based study of elderly Italian individuals for investigation of cognitive impairment epidemiology and risk factors. In women only, the highest homocysteine tertile was associated with incident depression. However, women with combined serum B12/folate deficiency had the highest blood homocysteine but also a lower depression risk than vitamin-repleted women. These data only moderately support the hypothesis that blood homocysteine is a predictor of depression [32].

Concerning plasma levels of homocysteine (second research question), our data show opposite results contrasting cross-sectional versus longitudinal analyses. Cross-sectionally, homocysteinemias increased with age, according to the literature, in different populations [1] [13] [33]. Viceversa, the listwise decreasing levels in homocysteine along the three waves in survivors may be likely attributable to the main causes of attrition. Indeed, in 1927 community-dwelling Chinese older adults aged 60 - 98 years, intrinsic capacity (IC) declines with ele-

vated homocysteine: in a J-shaped association of homocysteine levels with low IC, even relatively low concentrations as Hcy ≥ 8.53 μM/L might provide clinical implications for early identifying the risk of low IC [34].

Concerning the comparison between plasma homocysteine levels of males versus female in old community dwelling persons [third research question], our data, who show higher levels in males, are in keeping with the mainstream in the literature [1] [13]. Higher plasma homocysteine levels have been found also in male geriatric patients admitted into an acute care geriatric ward in Northern Italy. Among admitted patients aged 65 years and older, 74.2% of men and 68.9% of women had elevated homocysteine levels. Elevated total plasma homosysteine concentrations were associated with older age, male gender, increasing serum creatinine, lower Mini-Mental State Examination score, and disability [35].

The wide span of plasma HCY concentrations might somehow bias our results; yet such bias might be balanced, by tails in opposite directions, and mitigated through appropriate statistical approaches.

Both strengths and limitations of our study should be interpreted as from its intrinsic nature. Our enquiry pertains a cohort of community-dwelling people aged 70 to 75 years at baseline, living in a geographically defined setting. That might limit the external validity in terms of generalizability. More, the duration of the follow-up (8 years) has implied an attrition. Yet the multidimensionality and the robustness of our protocol, as well as the rate of participation, are strengths.

5. Conclusion

In our community-dwelling cohort, homocysteinemia plasma levels were not correlated with GDS scores nor were higher in elderly people with clinically relevant or subthreshold depression than in their peer without mood affections. Our results are not supportive of the "homocysteine hypothesis of depression". On the other hand, our data are in line with the mainstream of the literature about higher homocysteinemia levels in males than females, and the increase of concentrations with age, cross-sectionally. Yet, the listwise decrease of homocysteinemia levels along three successive waves might stress the role of high homocysteinemia as a marker of bad health. New researches are needed to better understand the role of Hcy for the health and survival of older people.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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